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PHYSIOLOGICAL OBSERVATIONS FOLLOWING DESCENT FROM PIKE'S PEAK TO COLORADO SPRINGS

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AMONG the numerous physiological observations on the influence of high altitudes upon man, only a few have dealt with the changes following the descent to the lower level, and these have been on men who have resided at the high altitude from a few days to five weeks. It has been interesting, therefore, to follow the changes in the blood, circulation, and respiration of a man who has lived long on the summit of Pike's Peak, altitude 14,109 feet.

Mr. Howard H. Robison,[1] the resident manager of the Summit House on Pike's Peak, very kindly consented to serve as the subject for this study. He has resided on the summit six months — from early in May to November — for seventeen consecutive years. He first went up when a young man in his early twenties. He is a man of athletic physique, excellent habits, and leads a very active life. He holds the record for the most rapid ascent ever made of the Peak, walking from Manitou to the summit, up the "Cog" railway track, a distance of 8.9 miles and a rise of 7485 feet, in 2 hours 31 minutes.

[1] The writer wishes here to express his sincere thanks to Mr. Robison for so kindly serving as subject for this study, and to Mr. Leon C. Havens for help with blood-counts and air analyses.

In 1912 he went to the summit the morning of May 8 and came down the evening of November 12. During this period of over six months he had been down only once and then for only one night. The first observations on him were made on the summit of the Peak October 12, 13, and 14. The first study in Colorado Springs, altitude 6000 feet, was on the morning following his descent.

An attempt was made to have the examination made at the same hour each day so that daily rhythms need not be considered. Observations were made at frequent intervals throughout a period of ten weeks, and to these have been added a few isolated examinations made at other times. Changes were followed carefully for the first six days after the descent. Mr. Robison then went on a hunting trip for two weeks to Lamar, altitude 5765 feet, and was available again for the investigation several times during the next ten days. December 12 to January 25 he spent at San Antonio, Texas, near sea-level, after which he subjected himself to further observations.

The Changes in the Blood

The changes in the percentage of haemoglobin, number of red corpuscles, total oxygen capacity, total volume of the blood, and specific gravity of the blood have been followed. The results appear in Table I. The total oxygen capacity and blood volume were determined by the carbon monoxide method of Haldane and Lorrain Smith.[2] Care was taken to allow at least twenty minutes to elapse, while the subject still continued to breathe into the confined space of the apparatus, after having received the carbon monoxide, so that the gas would distribute itself evenly throughout the body. The blood samples then taken were titrated in duplicate, and sometimes in triplicate, with a standardised carmine solution against a north light. The percentage of haemoglobin was determined by the Haldane-Gower's haemoglobinometer and the blood-counts were made with a Thoma-Zeiss haemocytometer. For the specific gravity a series of wide-mouthed bottles containing mixtures of glycerine and water of different densities was used.

[2] Haldane and Lorrain Smith: Journal of physiology, 1900, xxv, p. 331.

The changes that followed Robison's descent from the summit of Pike's Peak to Colorado Springs agree in general character with

TABLE I

OBSERVATIONS ON THE BLOOD OF MR. ROBISON

Date	Time of observation	Percentage of haemoglobin	Total oxygen capacity in c.c.	Percentage oxygen capacity	Total volume of blood in c.c.	Specific gravity	Red corpuscles per cu. mm. in millions	
Oct. 12, 1912	3 p.m.	148	—	27.4	—	—	(7.7)[1]	Summit of Pike's Peak
13	8.45 a.m.	150	—	27.8	—	—	(7.5)	
14	7.55 "	148	1101	27.4	4018	—	—	
Nov. 13	7.35 "	144	1062	26.6	3992	1.073	—	Colorado Springs
14	10.40 "	142	1085	26.3	4125	—	—	
15	7.45 "	145	—	26.8	—	1.073	—	
16	7.25 "	144	1088	26.6	4090	1.073	7.6	
17	7.20 "	147	—	27.2	—	—	—	
18	7.15 "	143	1125	26.5	4245	1.072	7.7	
Dec. 3	8.15 "	134	1050	24.8	4234	1.071	7.4	Colo. Springs after return from Lamar
5	8. "	134	—	24.8	—	1.071	7.6	
12	7.45 "	132	1054	24.4	4320	1.070	7.5	
Jan. 26, 1913	10. "	122	—	22.6	—	1.068	7.2	After return from sea-level
28	7.30 "	121	965	22.4	4308	1.068	7.2	
30	8.20 "	122	973	22.6	4305	—	—	
May 1	7.25 "	122	—	22.6	—	1.067	7.0	In Manitou three months, altitude 6620 feet

[1] Counts made in July and August, 1911.

those observed by Douglas, Haldane, Henderson, and Schneider [3] in the English-American Pike's Peak Expedition of 1911. They observed on themselves following their return to Colorado Springs that there was an *immediate* reduction in the percentage of haemoglobin, which fell in a day or two to about 110 per cent, which is near the normal for the altitude of 6000 feet. Simultaneously in them there was a distinct decrease in the total oxygen capacity of the blood, but this was not so marked as the change in the haemoglobin percentage. In each man, except one, the blood volume increased for thirteen days following descent, after which it returned to the normal for the lower altitude.

In Robison the blood changes delayed in appearing and then took place at a very slow rate. The percentage of haemoglobin did not clearly alter during the first six days. At the end of three weeks it had fallen from 148 to 134 or about 9.4 per cent. Nine days later it had only reached 132, so in one month it had not nearly approached the average for the altitude. Sometime during the next six weeks while Robison was near sea-level the haemoglobin fell to 122, the level to be maintained throughout the remainder of the stay at the foot of Pike's Peak. The previous winter Robison's percentage of haemoglobin fell from 145 on Pike's Peak to 116 at Manitou. This also is high, the average being 110 in men at 6000 feet. In 1912–13 the entire fall in the haemoglobin percentage was 17.6 per cent.

The destruction of haemoglobin and alteration in blood volume followed a somewhat different course than that observed in the English-American Pike's Peak Expedition. Two determinations of Robison's total blood volume and total oxygen capacity were made on Pike's Peak; unfortunately the figures, which were on a loose sheet of paper, for the titration in the experiment made October 13 were lost. An approximate estimate made at the time showed the results to agree well with the data of the 14th. Unlike the immediate change observed in Douglas, Haldane, and Schneider there was in Robison no destruction of haemoglobin during the first six days after his descent. However, while the total oxygen capacity remained stationary there was some diluting of the blood on the

[3] DOUGLAS, HALDANE, HENDERSON, and SCHNEIDER: Philosophical Transactions of the Royal Society of London, 1913, Series B, CIII, pp. 271–298.

sixth day which gave an increase of 5.4 per cent in the total blood volume. During the next three weeks the total oxygen capacity diminished 4.3 per cent; while on the other hand, the blood reached its maximum volume. This was 7.5 per cent greater than the volume on Pike's Peak. While Robison was at sea-level the blood volume does not appear to have increased. There was, nevertheless, during this period a marked destruction of haemoglobin; the total oxygen capacity of the blood the last of January was 11.9 per cent less than it had been on the summit of the mountain. Applying Hüfner's value that the amount of oxygen which combines with one gram of haemoglobin is 1.34 c.c. there were 822 grams of haemoglobin in the subject's blood on Pike's Peak. Sometime within the ten weeks he destroyed a surplus of 98 grams of haemoglobin.

The reductions in the number of red corpuscles and in the specific gravity of the blood are roughly parallel with the other blood changes.

Observations on the Arterial Pressure and Pulse-Rate

For six years at widely separated periods arterial pressure and pulse observations have been made on Robison, and these indicate that long residence at an extremely high altitude has in no way altered the efficiency of his heart action and circulation. The arterial pressure determinations were always made on the subject while resting in the sitting posture. They have been found to range as follows: —

	Systolic pressure	Diastolic pressure	Pulse pressure
On Pike's Peak	106 to 122 mm.	75 to 86 mm.	26 to 38 mm.
In Colorado Springs	114 to 126 "	80 to 90 "	28 to 39 "

A uniform difference in the pressures at the two altitudes has not been found. On the whole, however, the data agree with the observations of Schneider and Hedblom.[4] They found in a series of eighteen observations on Robison, in 1907, that his systolic and diastolic pressures averaged somewhat less on the summit of Pike's Peak.

[4] Schneider and Hedblom: This journal, 1908, xxiii, p. 101.

Robison's resting heart-rate on Pike's Peak during the three days October 12, 13, and 14 varied between 80 and 92 beats per minute. The normal tempo on Pike's Peak per minute as shown by frequent observations was about 82. The slowest rate yet noted in him at this high altitude was 68, recorded by Schneider and Hedblom in 1907.

A very marked slowing of the pulse-rate, such as was observed by Durig and Kolmer,[5] occurred following Robison's descent to Colorado Springs. During the first five days the rate remained constantly at 60 but on the sixth morning it had increased to 64. After the trip to Lamar the resting pulse had accelerated to 72 and throughout the remaining period of study it never returned to the slow tempo of the early days, but varied between 68 and 78. This increase in the pulse-rate does not appear to be definitely associated with the blood changes although the haemoglobin percentage had fallen ten points at the time the rate increased and the total oxygen capacity of the blood was slightly lowered. Very likely the explanation is to be found in the fact that the alveolar oxygen pressure in the lungs had fallen almost to the normal for the lower altitude.

Benedict and Higgins[6] have shown that the pulse-rate at sea-level in normal individuals breathing oxygen-rich mixtures is less than when breathing ordinary air. Parkinson [7] confirmed their observations and suggests in that the blood is capable of taking up more oxygen, when an excess is present, the heart muscle is better supplied with oxygen and thus works to better advantage, supplying the tissues by fewer beats. It is evident that the reaction of the organism to high altitudes is in large measure due to deficiency of oxygen and, therefore, we may expect the heart to benefit when oxygen is administered. This was found to be the case. Robison was set to breathing oxygen through the apparatus employed for administering carbon monoxide and oxygen in the blood volume studies. In each of two experiments on the summit of Pike's Peak there was almost an immediate slowing of the heart. Thus in the first experiment in two minutes after beginning to breathe the pure

[5] DURIG: Physiologische Ergebnisse der im Jahre 1906 durchgeführten Monte Rosa Expedition, p. 48.

[6] BENEDICT and HIGGINS: This journal, 1911, xxviii, p. 25.

[7] PARKINSON: Journal of physiology, 1912, xliv, p. 54.

oxygen his pulse-rate was reduced from 80 to 72 and at the end of seven minutes had fallen to 64. The second experiment a day later was briefer but again the pulse-rate after having remained at 82 for some minutes was reduced in two minutes to 72 and a minute later was down to 70.

During the first month after the descent to Colorado Springs repeated attempts were made to reduce the cardiac-rate with oxygen but without success. It should here be remarked that the normal individual at an altitude of 6000 feet will respond to the breathing of oxygen-rich mixtures by a slowing of the pulse-rate. In our laboratories we have often confirmed the earlier observations on healthy young men. For example, one subject after sitting quietly for ten minutes had a pulse-rate of 71; this was lowered to 62 during ten minutes breathing of pure oxygen and four minutes after return to air it had again accelerated to 70 per minute. In a majority of the men studied, the character of the pulse while breathing the oxygen changes, becoming fainter and softer. With Robison this change could not at first be noted with certainty. However, on January 28 and 30 after he returned from sea-level the character of the pulse while he breathed the oxygen, although the rate was still unaltered, was found by several observers to be softer.

A definite slowing of this subject's cardiac-rate was obtained in an experiment on May 1, five and one half months after the descent. For ten minutes his pulse remained constant at 68 per minute; he was then given oxygen for ten minutes and during this interval the rate varied between 64 and 62. After the return to air the rate slowly increased and within nine minutes it had returned to 68.

The observations indicate that the accelerated heart-rate observed in the majority of persons during residence at very high altitudes is one of the several adaptive responses to the influence of the shortage of oxygen. They furthermore may possibly offer a confirmation of Parkinson's explanation that an excessive supply of oxygen in the blood favors the heart muscle. That there was less oxygen available for oxidative processes in the blood at 14,000 feet was indicated by the decidedly dark color of the blood when it was drawn for examination; while in Colorado Springs the color

was always a good arterial red. In addition, the partial pressure of oxygen in the arterial blood was less at the high altitude. Thus Douglas, Haldane, Henderson, and Schneider[8] found the mean partial pressure of oxygen in the arterial blood on Pike's Peak to be 88.3 mm. while Douglas and Haldane [9] have shown the mean at Oxford to be 99.1 mm. Miss FitzGerald [10] has pointed out that the symptoms of oxygen deficiency at high altitudes are due not to the amount of oxygen in the arterial blood but to the partial pressure of this gas in the blood. When Robison came down to Colorado Springs there must have been, because of his deep breathing (this is discussed later) and of the high content of haemoglobin in the blood, much more oxygen rendered available by the rise in the partial pressure of the arterial oxygen. This excess of oxygen may have acted by destroying easily oxidizable substances which are very abundant in the blood at very high altitudes and even to some extent at sea-level.[11] The withdrawal of the stimulating action of these metabolites which may act through their hydrogen ion-concentration,[12] or the excess of oxygen alone,[13] reduced the heart-rate of Robison below his normal for the lower altitude; and inhalation of pure oxygen, therefore, failed to further slow the heart. Later the breathing was shallower and the total oxygen capacity of the blood less, hence the supply of oxygen in the blood was not sufficient to completely destroy these oxidizable metabolites, or to permit the heart to work as economically as during the early days after the descent. It was, therefore, then possible to show the heart-rate when oxygen was administered.

The Respiration

Lung Ventilation. — The ventilation of the lungs for those dwelling at high altitudes is greater than that of mankind living

[8] Douglas, Haldane, Henderson, and Schneider: *loc. cit.*, pp. 197–98.

[9] Douglas and Haldane: Journal of physiology, 1912, xliv, p. 331.

[10] FitzGerald: Philosophical Transactions of the Royal Society of London, 1913, Series B, CIII, p. 361.

[11] Douglas, Haldane, Henderson, and Schneider: *loc. cit.*, p. 300.

[12] *See* Feldman and Hill: Journal of physiology, 1911, xlii, p. 439.

[13] Mathison — Heart, 1911, II, p. 60 — finds in his study of the heart-block that the cardiac tissues are sensitive to want of oxygen.

at sea-level. It has been known since the researches by Haldane and pupils [14] that the volume of fresh air taken into the lungs per minute during rest is so regulated as to keep the partial pressure of carbon dioxide in the alveolar air practically constant for the individual. The carbon dioxide content of the alveolar air is, therefore, taken as an index of lung ventilation. A diminution of the alveolar carbon dioxide pressure indicates an increase in the lung ventilation, while an increase in carbon dioxide means a reduction in the alveolar oxygen pressure. A number of workers [15] have demonstrated that the alveolar carbon dioxide pressure falls, and as a consequence the volume of air breathed increases, with a diminution of atmospheric pressure. According to Douglas, Haldane, Henderson, and Schneider the alveolar carbon dioxide pressure required to excite the respiratory centre of man on Pike's Peak falls to about two-thirds that of the normal value at sea-level. This causes the breathing of 30 per cent more air per minute and an increase of 50 per cent in the alveolar ventilation.

The partial pressure of carbon dioxide in the alveolar air on Pike's Peak is about 27 mm. as compared with 40 mm. at sea-level.

A series of observations on Robison's alveolar air under resting conditions were made while he was on the Peak and at intervals for a period of five and a half months after his descent. Haldane's [16] gas apparatus was used for the analyses and the samples of alveolar air were obtained by the direct method of Haldane and Priestley.[17] Table II contains the results of this study. The figures as given are with two exceptions the average of the analyses of two samples.

The content of alveolar carbon dioxide and oxygen on Pike's Peak agreed closely with that obtained on the members of the

[14] HALDANE and PRIESTLEY: Journal of physiology, 1905, xxxii, p. 225, and DOUGLAS and HALDANE: *ibid.*, 1909, xxxviii, p. 420.

[15] *See* BOYCOTT and HALDANE: Journal of physiology, 1908, xxxvii, p. 25; WARD: *ibid.*, p. 378; DOUGLAS: *ibid.*, 1910, xl, p. 472; ZUNTZ, LOEWY, MÜLLER, and CASPARI: Höhenklima und Bergwanderungen, 1905, p. 428; DURIG: Über das Verhalten der Atemmechanik und der Alveolartension, 1910, p. 61; and DOUGLAS, HALDANE, HENDERSON, and SCHNEIDER: *loc. cit.*, pp. 206–220.

[16] HALDANE: Methods of Air Analysis, 1912, p. 47.

[17] HALDANE and PRIESTLEY: *loc. cit.*, p. 228.

TABLE II

Date	Barometer in mm. Hg.	Percentage of gases in dry alveolar air		Partial pressure of gases in mm. Hg. in alveolar air at 37° saturated with moisture		
		CO_2	O_2	CO_2	O_2	
Oct. 12, 1912	458	6.96	12.42	28.6	51.0	Pike's Peak
12	458	6.72	12.91	27.6	53.1	
13	457	7.16	12.34	29.4	50.6	
14	457	6.27	12.59	25.7	51.6	
Nov. 13	616	4.77	15.59	27.1	88.7	Colorado Springs
14	612	5.19	15.62	29.3	88.3	
15	613	5.44	14.90	30.8	84.3	
16	623	5.52	15.51	31.8	89.3	
17	620	5.46	15.37	31.3	88.1	
18	616	5.95	14.62	33.9	83.2	
Dec. 3	608	6.28	14.74	35.2	82.7	After return from Lamar
5	609	6.42	13.27	36.1	74.6	
12	615	6.93	13.26	39.4	75.3	
Jan. 26, 1913	613	6.98	12.39	39.5	70.1	After return from near sea-level
28	612	6.67	12.29	37.7	69.4	
30	614	6.89	12.65	39.1	71.7	
May 1	607	6.64	13.70	37.2	76.7	In Manitou three months

English-American Pike's Peak Expedition after they had been two weeks on the summit. The first sample of alveolar air which was taken from Robison fourteen hours, or the next morning, after his descent showed no change whatever in the carbon dioxide partial pressure. Hence he still continued to ventilate his lungs as much as on the summit of the Peak, which resulted in an alveolar oxygen pressure at least 35 mm. greater than he had on the summit and at least 10 mm. above that found in men acclimatised to the altitude of Colorado Springs. During the first six days following the descent the alveolar carbon dioxide pressure very gradually increased and as it did the ventilation decreased. However, on the sixth day the alveolar oxygen pressure was still more than 5 mm. above the normal for the altitude of 6000 feet.

The next two weeks while the subject was hunting near Lamar the decrease in lung ventilation must have greatly retarded, for on December 3, three weeks after the descent, the alveolar carbon dioxide content was 35.2 mm., which was still below normal; his normal for the altitude of Colorado Springs being about 37 mm.

Sometime between December 3 and 12 the carbon dioxide pressure reached normal and may have passed above if the reading 39.4 mm. may be regarded as correct and it is the result of several analyses. It was impossible to study this condition further because the subject left that day for the journey to near sea-level.

The observations made in January, immediately after the return from this journey, indicate that at sea-level he adapted his breathing so that the ventilation of the lungs was similar to that of the normal man at that level.

It appears that Robison readjusted his breathing on returning to the altitude of Colorado Springs after a residence of six months at 14,109 feet far more slowly than men who have sojourned only a few weeks at a high altitude. Thus Ward [18] after a residence of six days at Capanna Regina Margherita on Monte Rosa, altitude 14,965 feet, and Douglas, Haldane, Henderson, and Schneider after their sojourn of five weeks on Pike's Peak, on descending found an *immediate* response, by an increase in carbon dioxide pressure and lessened lung ventilation, to the rise in the barometric pressure. The time required for complete adjustment in the mem-

[18] WARD: Journal of physiology, 1908, xxxvii, p. 383.

bers of the English-American Expedition at 6000 feet was not determined because they later went down to sea-level. Here, however, they observed that the change became complete within two weeks of the day of leaving the summit of Pike's Peak.

This slow change in Robison's respiration suggests that some condition affecting the respiratory centre and due to the altitude stimulus, want of oxygen, becomes more permanently fixed by longer residence at the high altitude. This acquired condition or habit is then very slowly readjusted on return to a low level.

It has been suggested by Douglas, Haldane, Henderson, and Schneider [19] that the fall in alveolar carbon dioxide pressure at high altitude is due to diminished alkalinity of the blood. They deem it probable that the diminished alkalinity is not due merely to an excessive production of lactic acid, as is the case after muscular activity, but to some adaptive alteration in the regulation of blood alkalinity; this regulative function they attribute to the kidneys. "A slight and gradual adaptive alteration in what one may call the exciting threshold of alkalinity for the kidneys would explain the reduced fixed alkalinity of the blood in acclimatised persons."

Power to hold the Breath. — Mosso [20] found on Monte Rosa that the power to hold the breath voluntarily was less than in Turin. The subject of this report was able to hold his breath on Pike's Peak for not longer than 25 to 28 seconds but in Colorado Springs he was able to hold it 46 to 56 seconds. No change in the power to hold the breath occurred during the winter.

Vital Capacity. — It is a popular belief, also held by numerous medical men, that the chest is greatly enlarged by residence at high altitudes. Humboldt [21] claimed to find an increase in the capacity of the thorax among the inhabitants of the Andes, and Williams [22] reports an increase in the size of the chest as a result of a residence in high mountain resorts. With these exceptions

[19] DOUGLAS, HALDANE, HENDERSON, and SCHNEIDER: *loc. cit.*, p. 301.

[20] MOSSO: Life of Man on the High Alps, 1899, p. 201.

[21] HUMBOLDT: Voyage aux régions équinoctiales du nouveau continent, fait en 1799–1804, Paris, 1814.

[22] *See* STRAUCH: American Journal of the Medical Sciences, 1911, cxlii, p. 115.

all observers agree that for the majority of persons the vital capacity actually diminishes at high altitudes. Mosso [23] showed the members of his expedition had on Monte Rosa a vital capacity that was less than in Turin. Zuntz and his co-workers,[24] Durig,[25] and Fuchs [26] have confirmed Mosso's report.

The morning after Robison came down to Colorado Springs and frequently throughout the period of study his vital capacity was determined. The records of the first day taken at intervals of five minutes are 4000, 3975, 4120, and 4070 c.c. The second day shows 4225 c.c. The difference undoubtedly should be attributed to lack of experience with the spirometer and not to a change in the thorax. After his return from sea-level there was no change in the capacity.

Robison's endurance and strength as a mountain climber are certainly not to be explained by chest development as the following comparison with Born's[27] statistics of Yale men well shows:

	Robison	Track Athlete	Average Student
Height	68.3 in.	68.7 in.	67.8 in.
Weight	145.0 lbs.	143.5 lbs.	137.0 lbs.
Girth of Chest (normal)	34.2 in.	36.3 in.	34.4 in.
Girth of Chest (inflated)	35.8 in.	38.1 in.	36.0 in.
Vital capacity	4225. c.c.	4753. c.c.	3934. c.c.

Even though Robison is an active man and has lived at an altitude of 14,109 feet for six months during each of the last seventeen years his chest measurements, considering his height, compare not with the athlete but with the average student at sea-level.

The two keepers[28] of the Regina Margherita hut on Monte Rosa who remained from the beginning of July until the end of

[23] Mosso: *loc. cit.*, p. 342.

[24] Zuntz, Loewy, Müller, and Casperi: *loc. cit.*, p. 335.

[25] Durig: *loc. cit.*, pp. 54–60.

[26] Fuchs: Sitzungsberichten der Physikalisch-Medizinischen Sozietät in Erlangen, 1908, xl, p. 240.

[27] Born: Yale Alumni Weekly, April 1, 1908, pp. 1–5.

[28] Mosso: *loc. cit.*, p. 154.

September at an altitude of 14,965 feet and continually ascended and descended for provisions showed a similar chest development. Francioli with a height of 68.5 inches and weight 169.8 lbs. had a vital capacity of 4017 c.c.; while Quaretta, height 64.6 in., weight 154.4 lbs., had a vital capacity of only 3790 c.c.

Summary

1. The percentage of haemoglobin in the blood decreased very slowly after the descent from Pike's Peak, falling from 148 to 132 in 30 days and to 122 during the following six weeks.

2. The number of red corpuscles decreased from 7.7 to 7.0 millions; the specific gravity of the blood from 1.073 to 1.067.

3. The total volume of the blood showed an increase of 5.4 per cent on the sixth day and a maximum, 7.5 per cent, on the 30th day.

4. The total oxygen capacity of the blood did not alter the first six days. At the end of the third week it had decreased 4.3 per cent and at the end of 10 weeks had diminished 11.9 per cent.

5. During a period of six years the arterial pressure has remained normal.

6. The pulse-rate on Pike's Peak was about 82. The first days after descent it remained at 60 and later accelerated to 70.

7. The breathing of an oxygen-rich mixture slowed the heart-rate from 82 to 64 per minute on the Peak, but after the descent did not alter the rate the first ten weeks. Later at the lower altitude a slight reduction in the pulse-rate was obtained with oxygen.

8. The alveolar carbon dioxide pressure required to excite the respiratory centre did not alter immediately. After 24 hours it began to rise and increased slowly for 30 days, at which time it was above the normal for Colorado Springs. It later returned to the normal. For more than three weeks the amount of lung ventilation was excessive for the altitude of 6000 feet.

9. The power to hold the breath on Pike's Peak was one-half of that in Colorado Springs.

10. The vital capacity and chest measurements are not greater than those of men of similar physique at sea-level.

THE EFFECT OF WATER INGESTION ON THE FATTY CHANGES OF THE LIVER IN FASTING RABBITS [1]

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IN a paper entitled "Hydropic Changes in the Liver Cells of Rabbits," soon to be published by Dr. C. J. Bartlett and myself, mention is made that the peculiar picture described is not seen in fasting rabbits. It was to establish this point and to emphasize the fact, that the "hydropic" changes were probably due to hyperfunctional activity, that the work here outlined was undertaken.

Five rabbits were taken for experimentation, and emphatic instructions were given to the attendant not to feed them; but no instructions were given concerning water. Our rabbits are at all times given plenty of green stuffs, so the attendant as a rule finds no need of watering them, and it was this fact that caused him to neglect to water the rabbits placed under observation. The first and second rabbits were killed on the fourth and fifth day respectively, but showed nothing abnormal in gross. The third was killed on the seventh day, and showed a moderate degree of fatty change in liver. The liver was enlarged, quite yellow, softer than normal and tore easily. It was this unexpected condition coupled with the lack of water ingestion that resulted in the work here to be reported.

Twenty-seven normal rabbits were used. Of these, eleven were fasted from four to ten days, no water being given, and are here designated as "Group A." A second group of nine rabbits were fasted from four to fourteen days, but were given ordinary tap water, and are here called: "Group B." The last, a group of seven rabbits, were fasted five to eleven days, were given distilled water, and are here designated: "Group C."

[1] Read before the American Ass'n of Pathologists and Bacteriologists, in Washington, D.C., May, 1913.

The rabbits were separated into groups of three to five, and placed in clean cages, which allowed ample room for them to move about; but not room for excessive exercise. Water was placed in dishes for the animals that were to receive it. Most of the rabbits were weighed at the beginning and at the end of the experiment, and showed an average loss of two fifths their original weight, varying from between 250 to 600 grams. This average was the same for both the watered and unwatered animals.

The livers were examined in the fresh state with Sudan III in all cases. Frozen sections were also made and stained with Sudan III, haematoxylin and eosin, and tissue was fixed in Zenker's fluid and formalin for inbedding.

Eight of the first group of eleven rabbits showed a moderate or advanced fatty infiltration. These animals were fasted, with no water given, from five to ten days, were then killed, and autopsied immediately. The livers of these animals were quite yellow, flabby, almost semi-fluid in consistency, tore readily, and left considerable fat on the knife in cutting. Scrapings stained with Sudan III showed numerous small and large fat globules. Osmic acid gave positive test for fat where tried. Microscopically, with haematoxylin-eosin stain, the typical picture of fatty infiltration was seen, the more numerous fat vacuoles nearest the central veins. One animal of this group was killed at the end of four days. The liver showed nothing in gross, but gave a few fat globules when stained with Sudan III. Microscopically, the cells were somewhat smaller, coarsely granular, and showed here and there a few small vacuoles, which might have been interpreted as fat. The remaining two were animals that fasted seven and nine days respectively. These animals died. The livers showed a marked degree of coccidiosis and were quite congested. Scrapings stained with Sudan III and microscopical examination were negative.

Of the second group of nine normal rabbits deprived of food from four to nine days, water being allowed, only one showed a fair degree of fatty infiltration of the liver, and gave the Sudan III test. The livers of five others showed very slight vacuolations in the cells, microscopically with the use of the oil immersion. The cells were smaller and more granular and the nuclei

stained well. The livers did not give the Sudan III test in the fresh state, but microscopically the vacuoles mentioned might have been interpreted as fat. The remaining three animals of this group showed only a slight increase in size of the cells and a more granular cytoplasm than normal.

Of the seven that make up the third group of fasting animals, and which received distilled water, only one, an eleven-day rabbit, gave a positive Sudan III test, and was found to have a fair amount of fat microscopically. The others showed a slight vacuolation of the cells with the oil immersion, but did not give the Sudan III test. Of these rabbits, the one that showed the distinct fatty change, and one of those that showed vacuolations, were killed, all the others died. Most of the animals of this group showed a marked coccidiosis, which might have contributed to their deaths; but apparently did not favor fatty change.

Summing up the results obtained as shown in the accompanying charts, we find that nine of the eleven hungered and unwatered rabbits gave both the Sudan III test and the microscopic picture of fatty infiltration. This is in striking contrast to the findings in the rabbits fasting under the same conditions, but receiving water, wherein only two of the sixteen animals showed a fair amount of fat, evidenced both with Sudan III and the microscope; seven showed slight microscopic vacuolations, but gave no Sudan III test; and seven were entirely negative. Whether or not a greater percentage of watered fasting rabbits would show the fatty change, if more time were given them, is questionable. Offhand it would appear that it is not only a matter of time, in-as-much as six of the seven animals that were negative both to Sudan III and microscopical examination were kept under observation until death. It is worthy of mention in this connection that all of the last mentioned animals suffered from extreme coccidiosis, which must have at least hastened their deaths before fatty changes could develop.

The literature on this subject is very scant and conflicting. Statkewitch [2] and Nikolaides [3] and others have shown fatty changes in the livers of fasting dogs, cats, rabbits and guinea pigs; but

[2] MOTTRAM: Journal of physiology, 1909, vol. 38, page 281.

[3] GILBERT AND JANNIER: Quoted by Mottram.

regard a decided fatty change taking place only after prolonged hunger, and consider these changes to be degenerative in character. Water was given the animals during their fast.

On the other hand, Gilbert's and Jannier's [4] experiments show that only a very mild degree of fatty change is seen in rabbits fasting for one to eight and one half days. These investigaors do not regard the change as degenerative.

GROUP A

No.	Days	Killed or Died	Macroscopic Sud.	III.	Microscopic	F. or V.*
1	4	Killed	Normal	Sl. +	cells swollen, granular, few show vacuolation	F.
2	5	"	"	+	definite fatty vacuoles in cells	F.
3	7	"	Soft, friable; yellow color	+	definite, fatty infiltration	F.
4	9	"	Soft, friable, flabby, yellow color, coccidia	+	Moderate fatty infiltration	F.
5	9	"	Soft, friable, flabby	+	Good amount of fatty infiltration	F.
6	10	"	Soft, friable, mushy	+	Good amount of fatty infiltration	F.
7	10	"	Soft, friable, flabby	+	Good amount of fatty infiltration	F.
8	10	"	" " mushy	+	Moderate amount of fatty infiltration	F.
9	7	Died	Congestion and coccidiosis	—	Natural cell structure	—
10	8	"	" " yellow mottling	+	Moderately fatty	F.
11	9	"	Congestion and coccidiosis	−	Normal cell structure	—

* F = Fatty V = Vacuoles − = Negative

[4] MIKALAIDES: Archiv für Physiologie, 1899, page 518.

Mottram[5] claims that a marked degree of fatty infiltration is evident in fasting and watered rabbits, and guinea pigs in from twenty-four to forty-eight hours. He states that this change is

GROUP B

No.	Days	Killed or Died	Macroscopic Sud.	III.	Microscopic	F. or V.*
1	4	Killed	Pale, otherwise normal	—	Cells slightly swollen, more granular	F.
2	5	"	Normal	—	Slight vacuolation, with $\frac{1}{12}$" objective	V.
3	6	"	"	—	Fair vacuolation	V.
4	11	"	"	Sl. +	Cells quite vacuolated for fat globules	F.
5	12	"	Congested, otherwise normal	—	Cells granular, moderately vacuolated	V.
6	14	"	Very pale	—	Cells granular, moderately vacuolated	V.
7	14	"	Normal	—	Cells granular, slightly vacuolated	V.
8	11	"	Congested, coccidiosis	—	Congestion coccidiosis, cells normal	—
9	10	Died	" "	—	Congestion, coccidiosis, cells normal	—

microscopically visible, and uses the oil immersion for its demonstration.

In conclusion the following suggestions may be offered:

1. Fasting, unwatered rabbits, from four days and upwards, show a decided fatty infiltration of the liver, apparent in gross and microscopically.

2. Fasting, watered rabbits, from ten days and upwards, may

[5] STATKEWITCH: Archiv für experimentelle Pathologie, 1894, page xxxiii.

show similar changes in the liver, but the percentage of incidence is very low, as compared with that of the unwatered animals.

3. In half the number of the fasting, watered rabbits under observation, microscopic vacuolation was observed. This vacuolation may be interpreted as a fatty change, but the picture is by no means comparable to that seen in the non-watered animals.

GROUP C

No.	Died	Killed or Died	Macroscopic Sud.	III.	Microscopic	F. or V.*
1	5	Died	Congested, extreme coccidiosis	—	Cells normal, congestion	—
2	8	"	Congested, extreme coccidiosis	—	" " "	—
3	7	"	Congested, extreme coccidiosis	—	" " "	—
4	6	"	Congested, extreme coccidiosis	—	" " "	—
5	7	"	Congested, extreme coccidiosis	—	Cells smaller, more granular, occasional vacuole	V.
6	11	Killed	Pale color, otherwise normal	Sl. +	Moderate fatty infiltration	F.
7	11	"	Normal	—	Cells swollen and granular, slight vacuolation	V.

ON THE INFLUENCE OF MUSCULAR EXERCISE ON THE ACTIVITY OF BULBAR CENTRES

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MUSCULAR exercise is accompanied by certain very definite adaptive changes in the circulation and in respiration. That there is an increased heart rate is a matter of common experience. The increase has been studied in detail by Hering,[1] Bowen,[2] Cook and Pembrey,[3] and others.[4] An increase in arterial pressure has been demonstrated by Zuntz and Tangl [5] on dogs working in a tread-mill, and by MacCurdy, Bowen, Cook and Pembrey, and others on men.[6] An increase in the rate and depth of respiration is a familiar accompaniment of muscular exertion. This has been studied in great detail by Geppert and Zuntz.[7]

The mechanism of these adaptations remains obscure. Various factors may be involved in bringing them about, and the task of determining which of the several possible factors are actually responsible is by no means easy. In each of the adaptations we have to do with a bodily function governed by bulbar centres. These centres have been shown to be susceptible to influences reaching them either by way of the blood stream or over afferent nerves. Our first task is to decide, if possible, for each of the

[1] Hering: Archiv für die gesammte Physiologie, 1895, lx, p. 483.

[2] Bowen: Contributions to Medical Research, Ann Harbor, 1903, p. 462.

[3] Cook and Pembrey: Journal of physiology, xlv, p. 1.

[4] Lowsley: This journal, 1911, xxvii, p. 446.

[5] Zuntz and Tangl: Archiv für die gesammte Physiologie, 1898, lxx, p. 544.

[6] For references see Lowsley: *loc. cit.*, p. 446.

[7] Geppert and Zuntz: Archiv für die gesammte Physiologie, 1888, xlii, p. 189.

adaptive changes, the relative importance of the two great channels of influence. Hering,[8] Hunt,[9] and Bowen [10] have concluded that so far as cardiac acceleration is concerned the adaptation is mediated chiefly through the nervous system. Johannson [11] agrees with their view as to the mechanism of immediate acceleration, but offers evidence that the persistent increase in heart rate following exercise depends on stimuli conveyed to the bulb by the blood. Johannson's view has recently been supported by Mansfeld,[12] to the extent of making the blood an important agent in the persistent acceleration of exercise, although the latter author differs from Johannson as to the details of the mechanism.

When arterial pressure is considered we deal with a function depending only in part upon the activity of special bulbar centres, changes in heart rate and mechanical effects of muscular movement tending likewise to modify it. We cannot, therefore, draw direct conclusions as to the influence of exercise upon these centres from simple observations of blood-pressure changes. Bowen,[13] in fact, interprets the rise of blood pressure accompanying exercise on a basis wholly exclusive of vasomotor influences. Evidence that the vasoconstrictor centre is affected positively by exercise seems to be lacking, although Hooker [14] postulates a compensatory splanchnic vasoconstriction in accounting for the rise of venous pressure observed by him. There is, moreover, direct evidence of vasodilation within the active muscles,[15] perhaps dependent on activity of the vasodilator centre; and of cutaneous vasodilation in the later stages of prolonged exercise,[16] indicating a depression of the constrictor centre. Whether the mechanism for bringing about vasodilation in active muscles operates through nervous influences upon the vasodilator centre, or in some other way, has

[8] HERING: *loc. cit.*, p. 483.

[9] HUNT: This journal, 1899, ii, p. 464.

[10] BOWEN: *loc. cit.*, p. 462.

[11] JOHANNSON: Skandinavische Archiv für Physiologie, 1895, v, p. 20.

[12] MANSFIELD: Archiv für die gesammte Physiologie, 1910, cxxxiv, p. 598.

[13] BOWEN: This journal, 1904, xi, p. 60.

[14] HOOKER: This journal, 1911, xxviii, p. 235.

[15] KAUFMANN and CHAUVEAU: Archives de physiologie normale et pathologique, 1892, p. 283.

[16] BOWEN: *loc. cit.*, p. 69.

not yet been demonstrated. Masing [17] has shown that the cutaneous vasodilation occurring in prolonged exercise appears only when there is sweat secretion, suggesting a common, perhaps non-nervous, cause for the two phenomena.

The increased activity of the respiratory centre in exercise would seem, from the work of Geppert and Zuntz,[18] to be wholly explicable upon a non-nervous basis, as due to the presence of metabolites in the circulating blood.

Recapitulating the evidence thus far cited we note that the bulbar centres controlling the heart rate are influenced nervously during exercise so as to cause acceleration; that direct evidence for *nervous action* upon the vasoconstrictor and vasodilator centres is wanting, and the indirect evidence indicates no very striking influence; and that the respiratory centre is apparently unaffected during exercise by nervous influences.

So meagre a play of nerve impulses upon the medulla as here indicated seems strange when we consider on the one hand the demonstrated great susceptibility of the bulbar centres to afferent impulses in general, and on the other the great volume of nervous activity called into play during muscular exercise.

Such nervous influence upon the medulla as does accompany muscular exercise may possibly be of two sorts, associated innervation from the motor cortex, or reflex from excitation of organs of muscle sense in the active muscles. The possibility of associated innervation of the bulb during exercise seems to have been considered thus far chiefly with reference to cardiac acceleration. Johannson [19] believed that the immediate acceleration accompanying exercise is due chiefly to associated innervation. He based his view on the observation that experimental animals showed much more marked acceleration during voluntary struggling than during vigorous passive moments.

Athanasiu and Carvallo,[20] on the other hand, concluded from experiments on human beings suffering from paraplegia, in whom powerful but ineffective efforts toward movement brought about

[17] Masing: Deutsches Archiv für klinische Medicin, 1903, lxxiv, p. 253.

[18] Geppert and Zuntz: *loc. cit.*, p. 189.

[19] Johannson: *loc. cit.*, p. 20.

[20] Athanasiu and Carvallo: Archives de physiologie, 1898, xxx, p. 552.

no acceleration, that muscular exercise acts only reflexly in its effect upon the cardiac centres. They cite in support of their view the observation of Asp [21] that stimulation of the central end of nerves from skeletal muscles causes cardio-acceleration. Hering [22] considered both possibilities without arriving at any conclusion in favor of one over the other. Bowen [23] concluded that the increased pulse rate is partly cortical in origin and partly reflex.

We have undertaken the present investigation in the hope of throwing additional light upon the general problem of the reaction of the bulbar centres to muscular exercise and particularly in the attempt to determine whether or not the influence of muscular exercise is uniform in its effect upon the different centres.

The suggestion which we wish to offer as the result of our work may be stated in brief as follows: The immediate effect upon the bulbar centres of muscular exercise is due in the main to associated innervation from the motor cortex. This innervation acts to depress the cardio-inhibitory centre, the vasoconstrictor centre, and the respiratory centre.

The Depression of the Cardio-inhibitory Centre by Associated Innervation. — That the acceleration of the heart in exercise is due to depression of the inhibitory centre, rather than to stimulation of the augmentor centre, was well established by Hunt [24] on the basis of the short latent period of the acceleration as compared with the long latent period shown when the accelerator nerves are stimulated directly. Hering's earlier observation that the acceleration fails when the accelerator nerves are cut [25] is satisfactorily explained by Hunt [26] as showing the necessity for constant tonic activity of the augmentor centre to make depression of the inhibitory centre effective.

In the attempt to decide whether this depression of the inhibitory centre is cortical or reflex we have to consider the conflicting

[21] Asp: Ludwig's Arbeiten, 1867, p. 182.
[22] Hering: *loc. cit.*, p. 483.
[23] Bowen: Contributions to Medical Research, Ann Arbor, 1903, p. 462.
[24] Hunt: *loc. cit.*, p. 464.
[25] Hering: *loc. cit.*, p. 483.
[26] Hunt: *loc. cit.*, p. 464.

evidence of Johannson and of Athanasiu and Carvallo already cited. The position taken by these latter investigators seems to us to be not justified by their evidence. Powerful efforts toward movement on the part of paraplegic individuals do not necessarily result in a flow of impulses as far as the bulb, and in the absence of positive proof that impulses do reach the bulb, the experiment does not invalidate positive evidence on the other side.

We have attacked the problem of associated innervation vs. muscle reflexes, as accounting for the cardio-acceleration of exercise, in three different ways. Our first experiment was a repetition of Johannson's [27] observation on the influence of passive movements on heart rate. To avoid possible complications from the cortex we performed the experiment on a decerebrate cat. The form of exercise used was vigorous passive flexion and extension of both hind limbs, continued for about thirty seconds. We obtained acceleration of the heart in four of eight periods of exercise. The acceleration did not exceed 14 per cent in any case, and did not appear until after the exercise had been in progress at least five seconds. This latter observation we consider significant in view of the great promptness with which acceleration occurs in ordinary voluntary activity. [28]

Although passive movements of the joints give rise, undoubtedly, to considerable streams of afferent impulses, the objection may be offered that the impulses generated by passive movements are not necessarily equivalent to those aroused in the muscles during active contraction. Our second series of experiments was designed to overcome this possible objection. In these experiments we obtained vigorous active movements in two decerebrate cats by the use of strychnine. Our strychninized cats showed a rapid heart rate, ranging between 35 and 40 beats in ten seconds, but not by any means a maximal rate for the cat's heart; we have repeated observations of rates exceeding 44 beats in ten seconds. In twelve observations of the effect of strychnine convulsions on the heart rate we got acceleration in only three cases; not exceeding in any of them 9 per cent, and coming on more than ten seconds after the beginning of the convulsions.

[27] JOHANNSON: *loc. cit.*, p. 20.

[28] *See* BOWEN: *loc. cit.*, p. 462.

Our third series of experiments was a repetition of Johannson's original ones, except that we used human beings as subjects. The procedure was as follows: The subject lay flat on his back with legs extended. At intervals of one minute the pulse was counted for twenty seconds with a stop-watch. The subjects in these tests had been having their pulse counted regularly for several weeks, and were, therefore, presumably free from disturbing psychic reactions. After four or five minutes of preliminary pulse-counting the subject flexed his legs forcibly at the hips a designated number of times, leaving them extended again at the end of the exercise. The pulse was counted for twenty seconds beginning within two seconds after the body came to rest, and at minute intervals thereafter. For the passive exercise the subject's feet were grasped by an assistant and the legs alternately flexed and extended as vigorously as possible. The results obtained were as follows: Subject G. had for five minutes a pulse rate not exceeding 24 beats in twenty seconds. He flexed his legs four times; in the succeeding twenty seconds there were 26.5 beats. Three minutes later the rate was 23.5; two leg movements raised it to 26. Two minutes later, with the rate at 22, a single flexion of the leg brought about a rate of 25 in twenty seconds. Four minutes after this last reading the rate was 23.5; the legs were flexed passively one hundred times; the rate immediately afterward was 22.5. Two minutes later, with the heart rate at 22, the passive movements were repeated. The rate rose to 23. Two minutes after this last reading the rate had fallen to 21.5. A single active flexion of one leg raised the rate to 24. A second subject, M., showed precisely similar results. Prolonged passive exercise brought about no significant increase in heart rate, while one to four active leg flexions increased the rate three to four beats in twenty seconds.

The striking features of these experiments on human subjects were the marked acceleration resulting from very moderate amounts of active exercise, and the total failure of acceleration from vigorous passive exercise. Unless we deny absolutely the possibility that effective afferent impulses may be generated by passive movements, we must admit that these experiments point strongly toward associated innervation as the chief, if not the only, cause for the immediate acceleration of exercise. Our observa-

tions on decerebrate animals seem to us to point the same way, since neither vigorous passive movements nor the violent convulsions of strychnine brought about increases in rate at all comparable, either in amount, in promptitude, or in uniformity of occurrence, with the increases observed by Johannson and by ourselves in consciously active organisms.

An argument apparently in favor of the reflex source of the acceleration is that afforded by the well-known effect of posture on the heart rate, the erect posture being accompanied by a more rapid heart than is the recumbent. That this change of rate is not dependent on the increased muscular effort involved in maintaining the erect posture, but is due to the increased flow of blood to the lower parts of the body under gravity, was shown by Erlanger and Hooker.[29] In corroboration of their conclusion we can report the observation that even so marked a heightening of postural tonus as appears in decerebrate rigidity is without marked effect on heart rate. In two experiments on cats in which we compared the heart rate before decerebration with the rate after decerebration we had average rates of 18 and 15 beats in five seconds before, and of 16 and 15 in five seconds after the operation, and after rigidity had manifested itself.

The Response of the Vasoconstrictor Centre to Muscular Exercise. — The rise in blood pressure which accompanies muscular exercise is to be explained, as already noted, as due to mechanical effects of the exercise, together with the augmented heart beat. Whether direct nervous or chemical influences dependent upon muscular activity exert any effect upon the vasomotor centre has not been certainly determined. A fact noted by Lowsley [30] suggests that the metabolites poured out into the blood during exercise may depress the vasoconstrictor centre, as they were supposed by Johannson to depress the cardio-inhibitory centre. Lowsley observed that shortly after the cessation of activity blood pressure falls to a point lower than that obtaining before the exercise began. Since this lowered blood pressure cannot be referred to a diminished heart beat it signifies depression of vasomotor tone. The explana-

[29] Erlanger and Hooker: Johns Hopkins Hospital Reports, 1904, xii, p. 332.

[30] Lowsley: *loc. cit.*, p. 451.

tion proposed by Lowsley,[31] that this lowered blood pressure is due to fatigue of the centre following its great activity during the period of exercise, does not commend itself, in view of the probability that there is, as a matter of fact, little such activity. The observation of Bowen, already cited,[32] of cutaneous vasodilation during later stages of prolonged exertion, counts against the notion that the vasomotor centre is active during exercise, and may be looked upon, perhaps, as additional evidence pointing toward a depressor function for fatigue products.

While we have in metabolites carried by the blood a probably adequate mechanism for the vasomotor effects which follow exercise, these are too slow in operation to explain any reactions of the vasomotor centre that may occur at the outset of activity. If any such are normal accompaniments of exercise they are due to the operation of one or both the nervous mechanisms already noted as possible agents in bringing about bulbar responses, namely associated innervation, and muscle-sense reflexes.

A procedure which might be indicative of the existence of nervous influences affecting the vasoconstrictor centre during exercise would be stimulation of the motor cortex. Vasomotor responses to such stimulation might be supposed to represent the normal results of associated innervation during voluntary muscular activity. The earlier investigators who studied the effects of cortical stimulation on blood pressure obtained contradictory results.[33] Usually vasoconstriction with rise of blood pressure was observed, but in a number of cases a fall of pressure occurred instead. These observations were made upon curarized animals. Howell and Austin,[34] repeating the experiment, found that the effect varied with the anesthetic used. They obtained with dogs rise of pressure uniformly when morphia and curare were used, and fall of pressure when morphia and ether were used. We stimulated the motor cortex in several cats, using ether and morphia, and ether alone, and obtained uniformly a fall of carotid pressure.

[31] LOWSLEY: *loc. cit.*, p. 465.

[32] BOWEN: This journal, 1904, xi, p. 69.

[33] For early literature see TIGERSTEDT: Physiologie des Kreislaufes, Leipzig, 1893, p. 536.

[34] HOWELL and AUSTIN: This journal, 1900, p. xx.

The percentage drop varied from 16.7 to 35, averaging in fourteen observations 23.7. That this drop was due to vasodilation and not to diminished heart action is shown by the fact that in all but two of more than twenty-five observations the heart was slightly accelerated during the period of falling pressure. To determine whether the dilation was the result of depression of the constrictor centre or stimulation of the dilator mechanism we clamped the abdominal aorta, below the renal arteries, and also both axillary arteries, thus shutting the extremities out of the circulation. Repetition of the cortical stimulation gave a fall of carotid pressure as before, and the percentage change equalled that of our previous experiments. In another cat, whose splanchnic nerves had been cut sometime previously, in connection with another research, we stimulated the motor cortex repeatedly, recording blood pressure throughout. A slight drop in pressure accompanied each stimulation, not exceeding in any case eleven per cent, whereas in animals with intact splanchnics the least drop observed exceeded sixteen per cent, and the average was above twenty-three per cent. Since these procedures show the splanchnic area to be predominant as the seat of pressure changes, and since dilators to the splanchnic area have not been conclusively demonstrated, the evidence for splanchnic vasodilators depending at present solely on the observations of Dale,[35] we interpret our results as indicating an associated innervation from the motor cortex, depressor to the vasomotor centre. A criticism which might be urged against this conclusion is that we have accepted the results of cortical stimulation with ether anesthesia, and rejected contrary results obtained with curare-morphia anesthesia, because the former fit our theory and the latter do not. In reply to such a criticism we would state that our laboratory experience with ether and with curare, together with some observations to be published in due time, indicate that in ether anesthesia the behavior of reflex mechanisms corresponds in kind, although not in degree, with their behavior in decerebrate unanesthetized animals, whereas under curare the responses are often different in kind as well as in degree. The very fact that diametrically opposite results are obtained from cortical stimulation under these two drugs shows that one or both of them brings

[35] DALE: Journal of physiology, 1913, xlvi, p. 291.

about profound modifications in the nervous mechanisms involved. In our opinion curare probably has this effect, and for that reason we are inclined to question the soundness of many observations on vasomotor reactions in which curare was employed.

FIGURE 1. Blood pressure curve during a strychnine convulsion. The upper signal line shows the period of the convulsion. The lower line indicates time — 5 second intervals.

As a means of determining whether a definite immediate effect of exercise on the vasomotor system can be demonstrated in animals in which cortical influences have been excluded, we made a number of observations on decerebrate cats. One method of inducing vigorous activity in these animals was by the use of strychnine. Decerebrate cats dosed with strychnine (.3 mg. in 3 c.c. saline) show typical convulsions. The blood-pressure changes observed during these convulsions were in some of our experiments such as to suggest more than mere mechanical effects from the strongly contracted muscles. A typical curve is presented in Fig. 1. During the convulsion there was a sharp rise in pressure followed immediately by a rapid and extensive fall. Had these been purely mechanical effects there should have been, with cessation of the spasm, a rapid return of pressure to normal, such as occurs, for example, after a lowering of pressure by squeezing the thorax. Instead of such a rapid return, the pressure rose gradually, requiring thirty seconds to reach normal, and suggesting recovery from depressor stimulation. Pressure changes similar to those shown in Fig. 1 occurred in two of our strychninized decerebrate cats. In a third cat, dosed with excessive amounts of strychnine (3 mg.), each spasm was accompanied by a marked rise of pressure, ap-

parently mechanical, with a prompt return to normal after the spasm, and without a secondary fall. In still another cat, given the usual strychnine dose (0.3 mg.), no marked blood-pressure changes occurred, although the convulsions appeared to be of as great intensity as in our other experiments.

While these observations point to a possible reflex depression of the vasoconstrictor centre during the muscular spasms induced by strychnine, they were not constant enough to establish such an effect definitely, nor do they yield much information concerning the response of the normal animal, since the strychnine poisoning may well have brought about profound variations from the normal functioning of the nerve centres.

Another method of initiating from the muscles reflexes which might affect the vasoconstrictor centre was by the use of passive movements of the limbs. These we tried also upon decerebrate cats. In four trials we observed very slight lowering of pressure with gradual recovery, and in three other tests no pressure change whatever.

So far as our observations on blood pressure suggest anything they point to associated innervation as a more important influence than muscle-sense reflexes, and indicate depression of the vasoconstrictor centre as the effect produced. Physiologically such an effect might be of value as a protection against the excessive arterial pressure which would normally follow the augmented heart and the mechanical influences of exercise.

The Effect of Exercise on the Respiratory Centre. — We have already cited the conclusion reached by Geppert and Zuntz that the heightened activity of the respiratory centre during and after exercise is mediated through the blood rather than through nervous influences. In connection with our studies of muscular exercise we have made some observations on the immediate respiratory changes which accompany it. These, on account of the promptness of their onset, can scarcely be due to influences exerted through the blood stream. One form of exercise selected for this study was the lifting and sustaining of heavy weights, in some cases by flexing the arm at the elbow, in others by lifting with both arms a bar on which weights were hung. We adopted this form because it involves intense voluntary innervation of the active muscles without

calling into play so large a bulk of muscle tissue as to flood the system immediately with metabolic products. Respiration was recorded by means of a Fitz pneumograph about the chest, communicating with a recording tambour. Our subjects, except two, were ignorant of the meaning of the experiment, and of the significance of the apparatus used. They were chosen thus to avoid, as far as possible, the modifications in breathing which are apt to occur when the subject gives attention, voluntarily or involuntarily, to the act.

In sixteen observations, with weights ranging from 4 to 10 kilos, lifted with the left arm, there was a slowing of respiration in ten cases, an increase of rate in five, and no change in one. All the cases of increased rate, save one, occurred in experiments upon subjects who were aware of the nature of the procedure, and interested in the outcome.

When the subjects lifted heavy weights (25–50 kilos) with both arms the respiratory behavior was uniformly as follows: at the signal for beginning the effort a deep inspiration was taken; then with the glottis closed and the abdominal muscles tense the weight was lifted and held. During several seconds no respiratory activity was manifested. When, after this period of cessation, breathing was resumed, it proceeded at the normal rate, but the individual breaths were abruptly drawn and shallow and the chest was held throughout the period of effort more or less in the inspiratory position through the sustained contraction of the abdominal muscles.

Further evidence as to the respiratory behavior during intense muscular effort was had by questioning athletes with reference to their practice during the vigorous running competition known as the short dash. A common feature of indoor games is a forty-yard dash. So far as we could learn, the invariable habit of participants in this event is to refrain from breathing throughout its progress, except for a quick inspiration taken sometimes at the instant of starting. In the hundred-yard dash there is usually cessation of breathing during the first forty yards or so of the distance, then two, or sometimes three, hurried breaths are caught in rapid succession, and during the final rush for the goal the breath is held again. An interesting bit of incidental testimony is

that the closer the contest, and therefore the more intense the struggle, the more tendency is there for the breath to be held.

The observations we have cited seem to us to show clearly that during intense muscular effort there is a tendency toward inhibition of the respiratory centre. There is, to be sure, in nearly every case a preliminary drawing of breath, but this, so far as we can judge, is primarily of importance as a means of fixing the trunk muscles in the position most favorable for the effort, and only secondarily of respiratory significance. These respiratory modifications are obviously not voluntary in the ordinary sense, since they may occur without the conscious knowledge of the subject, and while his mind is engrossed with the muscular effort he is making, and since they become more marked the more complete is the engrossment in the effort. On the other hand, if one observes his breathing during the performance of intense exercise the impression is strong that the effort of holding the breath is part of the general effort involved. The inhibition of the respiratory centre through associated innervation, postulated by us in the opening paragraphs of this paper to account for the change of breathing occurring at the outset of exercise, seems to us to offer a reasonably satisfactory device for beinging about the effect observed. Associated cortical innervation acting upon a system of ordinary motor nerves and skeletal muscles such as is the respiratory mechanism might be expected to give the impression in consciousness of voluntary effort when attention is directed to it, and to operate unconsciously under ordinary circumstances.

From the standpoint of respiration an inhibition of the centre during intense muscular effort is obviously not adaptive. From the standpoint of the exercise, however, the fixation of the trunk in the inspiratory position may well be advantageous. There is no danger that the body will suffer from the suspension of breathing, for the rapid accumulation of metabolic products presently overcomes the cortical inhibition of the centre, with resumption of breathing and hyperpnea.

SUMMARY

1. The view of Johannson that the immediate cardio-acceleration of exercise is due to associated innervation from the motor cortex is supported, and additional evidence in favor of it is presented. This evidence consists of experiments on decerebrate cats in which vigorous passive movements or activity induced by strychnine produced no noteworthy change in heart rate; and on men, in which passive movements, producing no change in heart rate, were contrasted with moderate voluntary movements, which resulted in marked cardio-acceleration. On the basis of observations of Hunt and Bowen this acceleration is interpreted as due to depression of the cardio-inhibitory centre.

2. The assumption is made that the vasoconstrictor centre is depressed by associated cortical innervation during muscular activity. In support of this assumption the fall of pressure accompanying stimulation of the motor cortex is cited, and evidence is presented showing that this is due to depression of the vasoconstrictor centre and not to active vasodilation.

3. On the basis of observations of breathing during weight-lifting and during sharp running we conclude that there may be a cortical inhibition of respiratory activity during periods of intense motor innervation, not voluntary in the ordinary sense, but rather the result of associated innervation.

4. The conclusions cited in the above paragraphs are grouped into the general assumption that during muscular exercise there is associated innervation to the bulb, depressor to the cardio-inhibitory, the vasoconstrictor, and the respiratory centres.